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HEALTH TECHNOLOGY BRIEFING
JUNE 2020

Potassium citrate and potassium bicarbonate for distal renal tubular acidosis – first line

NIHRIO ID	19352	**NICE ID**	9790
Developer/Company	Advicenne	**UKPS ID**	653889

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

ADV7103 is a combination product of potassium bicarbonate + potassium citrate extended release (i.e. the drug is released slowly over time). It is intended to treat distal renal tubular acidosis (dRTA) in adults, adolescents and children aged 6 months and older. DRTA disease occurs when the kidneys do not properly remove acids from the blood into the urine. As a result, too much acid remains in the blood (called acidosis). It can lead to many health problems and can vary in severity. Currently there are no approved treatments specifically for this condition.

ADV7103 is an innovative product with a prolonged-release formulation, designed to maintain sustained release over a twelve-hour period for dRTA treatment. As the combination is alkaline (pH greater than 7) and contains potassium, it is expected to neutralise excess acid in the blood and restore levels of potassium. The product was developed as a multi particulate formulation in 2mm granules that contains two active pharmaceutical ingredients. Bicarbonate + potassium citrate is tasteless and easy to administer, in small-size format that offer flexible, personalized dosing which makes it easier to take for patients of all ages. The ability of ADV7103 to normalize biological disorders caused by dRTA throughout the course of treatment has been shown in a Phase III extension study. If licensed, ADV7103 will offer a potentially curative treatment option for patients with dRTA, who currently have few approved therapies available.

PROPOSED INDICATION

First line treatment of distal renal tubular acidosis (dRTA) in adults, adolescents and children aged 6 months and older.[a]

TECHNOLOGY

DESCRIPTION

The medicine is a combination of two salts, tripotassium citrate monohydrate (also known as potassium citrate) and potassium hydrogen carbonate (also known as potassium bicarbonate), that are taken by mouth and released slowly into the body over a few hours. Because the combination is alkaline and contains potassium, it is expected to both neutralise excess acid in the blood and restore levels of potassium.[2] This is significant for people with dRTA, which is characterised by their kidneys' inability to effectively filter acids from their blood, resulting in acid buildup and hypokalemia. [3]

Potassium bicarbonate and potassium citrate have completed their EU phase III clinical development program as a therapy for the treatment of dRTA in adults, adolescents and children aged 6 months and older. In phase III clinical trial (NCT03644706), patients were given a fixed ratio of 1/3 of potassium citrate and 2/3 of potassium bicarbonate, receiving them twice a day for up to 21 weeks. The strength is 6.44 (± 10 %) mEq/g of ADV7103 (alkalinizing power). [4]

INNOVATION AND/OR ADVANTAGES

ADV7103 is tasteless and easy to administer, in small-size format that offer flexible, personalized dosing which makes it easier to take for patients of all ages [5]

Preliminary results of a Phase III extension study of an open-label clinical trial confirm the efficacy and safety of ADV7103 after 24 months of treatment. Results from 90% of patients at 6 months, 12 months, 18 months and 24 months demonstrate the ability of ADV7103 to normalize biological disorders caused by dRTA throughout the course of treatment. This efficacy, measured by blood bicarbonate levels and stabilized serum potassium, remains constant in about 80% of patients. [6] If licensed, ADV7103 will offer a potentially curative treatment option for patients with dRTA, who currently have few approved therapies available.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

ADV7103 does not currently have Marketing Authorisation in the EU/UK for any indication.

In 2017, ADV7103 was awarded as an orphan drug in the EU for distal renal tubular acidosis.[2]

Additionally, ADV7103 is in phase II clinical development for cystinuria[7,8] (inherited condition characterized by a buildup of the amino acid, cystine, in the kidneys and bladder[9]).

[a] Information provided by Advicenne on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Distal renal tubular acidosis (dRTA) is a disorder of impaired net acid secretion by the distal tubule characterized by hyperchloremic metabolic acidosis.[1] It occurs when the kidneys fail to excrete acids into the urine, which causes a person's blood to remain too acidic. [10]

DRTA can be acquired or inherited. Hereditary dRTA subtypes include autosomal dominant (AD) and autosomal recessive (AR) dRTA. AD dRTA is usually due to mutations in the SLC4A1 gene (17q21.31). Mutations in the ATP6V1B1 gene (2p13) or ATP6V0A4 gene (7q34) are responsible for AR dRTA with deafness. AR dRTA without deafness or late onset deafness has been mainly described in patients with mutations in the ATP6V0A4 gene but overlap does exist in that some patients with this mutation develop deafness and others do not. Acquired forms of dRTA are thought to be caused by autoimmune diseases such as Sjögren syndrome or secondary to other conditions like sickle cell anemia, systemic lupus erythematosus, chronic obstructive uropathy, or post-renal transplantation.[1]

Primary dRTA is a highly variable disorder and can affect people very differently. In the cases of incomplete forms of dRTA, which refer to a condition when stone formers cannot acidify urine of pH less than 5.3 during acid loading, most individuals may only have slightly elevated acid levels and no accompanying symptoms (asymptomatic).[11] However, many individuals living with primary dRTA may experience kidney stones and others may not. Generally, people with an autosomal dominant pattern of inheritance have milder symptoms and a later age of onset of symptoms than people with an autosomal recessive pattern of inheritance. However, this is not always true and sometimes more severe complications such as growth failure or rickets (bowing of the bones), can affect individuals with dominantly-inherited primary distal renal tubular acidosis. [12]

Other severe consequences of dRTA include: nephrocalcinosis (refers to excesses deposition of calcium in the kidneys[13]) and nephrolithiasis[14] (process of forming a kidney stone, a stone in the kidney, or lower down in the urinary tract[15]) vomiting, profound dehydration and obtundation (altered level of consciousness). [16]

CLINICAL NEED AND BURDEN OF DISEASE

At the time of designation (2017), distal renal tubular acidosis affected approximately 2.1 in 10,000 people in the European Union (EU). This was equivalent to a total of around 108,000 people, and is below the ceiling for orphan designation, which is 5 people in 10,000. [2]

UK patient population range between 1 per 50,000 and 25 per 100,000.[b]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The main treatment for dRTA involves alkali agents, which are used to reduce acid buildup in the blood. Alkali agents can include sodium bicarbonate, potassium bicarbonate, sodium citrate or potassium citrate. [3]

Alkali therapy is the standard treatment (to achieve normal serum bicarbonate levels). Patients are usually given sodium bicarbonate or sodium citrate. Children require very high doses (4-8

[b] Information provided by Advicenne on UK PharmaScan

meq/kg/day) whereas adults need much lower doses (1-2 meq/kg/day). Potassium replacement is also necessary in hypokalemic patients and potassium citrate is usually recommended. The dose depends on the severity of hypokalemia. Hyperkalemic types require low dietary potassium intake and other therapies. [1]

CURRENT TREATMENT OPTIONS

Current treatment/management options for distal renal tubular acidosis include the following:

- Sodium bicarbonate or sodium citrate [17]
- Potassium bicarbonate or potassium citrate [17]

PLACE OF TECHNOLOGY

If licensed, ADV7103 will offer the only licensed treatment option for dRTA for adults, adolescents and children aged 6 months and older.

CLINICAL TRIAL INFORMATION

Trial	**NCT03644706, A Phase 3 Multicenter, Randomized, Double-Blinded, Placebo-Controlled Withdrawal Study Evaluating ADV7103 In Pediatric and Adult Subjects With Distal Renal Tubular Acidosis (dRTA)** **Phase III - ongoing** **Location(s): USA and Canada**
Trial design	Randomized, Double-Blinded, Placebo-Controlled Withdrawal Study
Population	N=40; female or male subjects ≥ 6 months of age and ≤ 65 years of age at time of consent, previous diagnosis of primary dRTA of at least 4 months duration for subjects < 12 years of age, and at least one year for those ≥ 12 years of age
Intervention(s)	ADV7103, administered orally, twice a day for six days
Comparator(s)	Placebo (patients receive matched placebo twice a day until they reach a bicarbonate level of 18mEq/L)
Outcome(s)	Mean change in blood bicarbonate levels [Time frame: 6 days]
Results (efficacy)	-
Results (safety)	-

Trial	**EudraCT-2013-002988-25, A multicentre, open-label, non-inferiority sequential study, evaluating the efficacy, safety, tolerability and acceptability of ADV7103 compared to standard of care in distal renal tubular acidosis patients** **Phase II/III - completed** **Location(s): Belgium, France, Italy, Serbia, Slovakia, Spain, United Kingdom**
Trial design	Multicentre, open-label, non-inferiority sequential study
Population	N=37; Male or female, including children aged between 6 months and 17 years old and adults aged between >18 years and <55

	years old; diagnosed with dRTA (acquired or inherited) with metabolic acidosis
Intervention(s)	ADV7103, administered orally, up to 10 mEq/Kg milliequivalent(s)/kg, twice per day for five days
Comparator(s)	Standard of care (SoC)
Outcome(s)	Average bicarbonate blood level during 3 days of treatment at steady state with ADV7103 and SoC
Results (efficacy)	14/17 of non-responders for bicarbonataemia previously treated with so called SoC became responders when switching to ADV7103 (82.4%) [18]
Results (safety)	-

Trial	**EudraCT-2013-003828-36, A multicentre, open-label, extension study, evaluating the safety and tolerability and the efficacy of ADV7103 at long term in distal renal tubular acidosis patients. Phase III** **Location(s): France, Serbia, Slovakia, Spain**
Trial design	Multicentre, open-label, extension study
Population	N=24; Participants included those that participated and completed the previous Advicenne clinical trial (B21CS)
Intervention(s)	ADV7103, administered orally for long term (precise trial duration is not stated), dosage is not reported
Comparator(s)	-
Outcome(s)	Number/proportion of subjects presenting adverse events during the course of the study, including the incidence and severity of the adverse events
Results (efficacy)	Preliminary results of the Phase III extension study, an open-label clinical trial, confirm the efficacy and safety of ADV7103 after 24 months of treatment. Results from 90% of patients at 6 months, 12 months, 18 months and 24 months demonstrate the ability of ADV7103 to normalize biological disorders caused by dRTA throughout the course of treatment. This efficacy, measured by blood bicarbonate levels and stabilized serum potassium, remains constant in about 80% of patients.[19]
Results (safety)	-

ESTIMATED COST

Cost of ADV7103 was confidential at the time of producing this briefing.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

No relevant guidance identified.

ADDITIONAL INFORMATION

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.